## REMARKS

In the previous Office Action, the Examiner withdrew Claims 1-6 from further consideration as being drawn to a nonelected invention. Claims 7-8 are pending herein and stand rejected. Claim 8 is amended herein.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 7-8 under 35 U.S.C. § 112, first paragraph, "as failing to comply with the written description requirement." Specifically, the Examiner maintains that the "specification defines the phrase non-immunogenic, high molecular weight compound as being any compound 1000 Da or more that typically does not generate an immunogenic response and recites polyethylene glycol, polysaccharides, polypeptides, magnetic structures and even other nucleic acid ligands as examples of such compounds." Office Action, page 3.

The Applicants would also like to point out either a possible misconception of the invention or a typographical error on the part of the Examiner. The Examiner states, "the claimed invention is directed to improving the pharmacokinetic properties and drug delivery ability of a nucleic acid ligand by conjugating the ligand to a compound that is a high molecular weight non-immunogenic compound and administering the complex to the patient." The Examiner has omitted "Lipophilic Compound" from this statement. Lipophilic compounds are listed in claims 7-8 alongside with a high molecular weight non-immunogenic compound. Accordingly, Applicant would like the record to reflect that the claimed invention is directed to conjugating the nucleic acid ligand to a compound that is a high molecular weight non-immunogenic compound or a lipophilic compound.

With respect to Claim 7, the Examiner contends that "the specification provides some general guidance of what would be included in the genus, but there is no structure demonstrated in the specification or known in the art to correspond with the function of being a non-immunogenic, high molecular weight compound. [PEG] is recited as an example . . . but the structure of PEG does not lead the skilled artesan to the structure of other compounds such as polysaccharide or magnetic structures that would be non immunogenic."

In response, Applicants first discuss the law and USPTO Office guidelines for written description. For example, case law shows that "[t]he test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession of the claimed subject matter, rather than the **presence or absence of literal support** in the specification for the claim

language." *Ex Parte Harvey*, 3 USPQ2d 1626, 1627-28 (B.P.A.I. 1987) (Emphasis added). "The written description must communicate that which is needed to enable the skilled artisan to make and use the claimed invention." *In re Wilder*, 736 F.2d 1516, 1520, 222 USPQ 369, 372 (Fed. Cir. 1984). It is sufficient that the specification "convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that the applicant has invented the specific subject matter later claimed." *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 97 (C.C.P.A. 1976) (emphasis added). For original claims, there is a **strong presumption that an adequate written description of the claimed invention** is present when the application is filed. *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) (Emphasis added).

The Guidelines for Examination of Patent Applications under the 35 USC § 112, 1st paragraph, "Written Description" Requirement, MPEP § 2163 II.A.3(a) (hereinafter, "Written Description Guidelines") state:

> Whether the specification shows that applicant was in possession of the claimed invention is not a single, simple determination, but rather is a factual determination reached by considering a number of factors. **Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone** or coupled with a known or disclosed correlation between structure and function, and the method of making the invention. **Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient** [citing Eli Lilly, 43 USPQ2d at 1406]. Patents and printed publications in the art should be relied upon to determine whether an art is mature and what the level of knowledge and skill is in the art. **In most technologies which are mature, and wherein the knowledge and level of skill in the art is high**, a written description question should not be raised for original claims even if the specification discloses only a method of making the invention and a function of the invention [citation omitted]. [emphasis added]

In the instant case, Applicants submit that, as reflected by the high number of related U.S. patents and printed application publications, the level of skill in the art is high and the art is mature with respect to the use of Lipophilic Compounds and/or High Molecular Weight Non-immunogenic Compounds, for improving pharmacokinetic properties of drug delivery and diagnostic targeting. Accordingly, less disclosure will be sufficient for satisfying the written description requirement. As discussed in the Guidelines (above), the Examiner can conclude that the maturity of the art is high, as evidenced by the fact that at there are over 570 issued patents in the United States alone with the phrase "liposome" in their abstracts, and over 1720 issued

patents in the United States alone with the phrase "polyethylene glycol" in their abstracts (using the USPTO's Full-Text database), most of which have priority dates prior to Applicants'. Further, using the search term "non-immunogenic AND "high molecular weight") AND conjugate", 298 records were returned from the issued patents (U.S. Patents) database. Again, a significant number of these patents have priority dates preceding Applicants'.

Thus, an examination of the U.S. patents database indicates that the art of conjugating Lipophilic Compounds and/or High Molecular Weight Non-immunogenic Compounds to therapeutically active compounds is very well developed. Further to Applicant's argument, there are a significant number of these types of conjugates in both preclinical and clinical trials for therapeutic indications, as well a number of conjugates approved by the Food and Drug Administration for therapeutic administration to humans. For example, there are numerous drugs formulated with Lipophilic Compounds and/or High Molecular Weight Non-immunogenic Compounds currently on the U.S. market. As the process of obtaining FDA approval takes many, many years, it is clear that workers have been developing such compounds for a number of years.

FDA-approved drugs include the following approved by 2005: ABELCET® (liposomal formulation of amphotericin B) sold by Enzon, AMBISOME® (liposomal amphotericin B) sold by Gilead Sciences, Inc., and Fujisawa Healthcare, AMPHOTEC® (lipid-based colloidal dispersion of amphotericin B) InterMune Pharmaceuticals, Inc., DAUNOXOME® (liposomal form of daunorubicin) sold by Gilead Sciences, DEPODUR (morphine sulfate extended-release liposome injection) sold by Endo Pharmaceuticals, Inc., and SkyePharma plc, DOXIL® (liposomal formulation of doxorubicin hydrochloride) sold by Alza (subsidiary of Johnson & Johnson), ESTRASORB™(Estradiol topical emulsion) sold by Novavax, Inc. and King Pharmaceuticals, Inc., IMAGENT® (perflexane lipid microspheres) sold by Alliance Pharmaceutical Corp., Cardinal Health, Inc. and InChord Communications, Inc., MACUGEN® (pegaptanib sodium injection; pegylated anti-VEGF aptamer) sold by Eyetech Pharmaceuticals, Inc. and Pfizer, PEGASYS® (peginterferon alfa-2a) sold by Roche and Nektar Therapeutics, Inc., PEG-Intron™ (pegylated version of interferon alfa-2b) sold by Enzon, Inc., and Schering-Plough Corp. (*see* Biotechnology Industry Organization, www.bio.org). Each of these new drugs have been in development for a number of years, indicating this art area's longstanding mature standing. This listing includes drugs directed to the modification of nucleic acid ligands to improve characteristics on the ligand such as improved *in vivo* stability or improved delivery characteristics (e.g., Macugen®).

As shown by the numbers of patents and patent applications, and approved drugs on the market, use of Non-Immunogenic, High Molecular Weight Compounds and Lipophilic Compounds for formulating therapeutics is a mature technology where the level of skill is high and advanced. In technologies which are mature, and where the knowledge and level of skill in the art is high, the Written Description Guidelines provide (see above) that a written description question should not be raised.

Turning to the instant application, Applicants have disclosed use of a Non-Immunogenic, High Molecular Weight Compound and Lipophilic Compound. The specification discloses a **large number** of exemplary Non-Immunogenic, High Molecular Weight Compounds and Lipophilic Compounds, such as, for example, the compounds cholesterol, phospholipids, glycerolipids, glycerol amide lipids, liposomes, polyalkylene glycol (including polyethylene glycol), and the like. A structure-function relationship is not necessary to allow for the skilled artesan to be led from Applicants' recited compounds and description of the genus to other compounds that have the recited functions and structures. For example, the art contains numerous well known non immunogenic compounds, such as the ones recited by applicants. A large number of compounds are known in the art which may be used for coadministration of therapeutics and/or diagnostics, and the immunogenicity of these compounds has previously been established by prior workers. In view of this well known and well developed art, and representative compounds disclosed by Applicants, the terminology used by Applicants is sufficient for the skilled artesan to understand that the Applicants had possession of the invention.

Further, the guidelines state that where the skill in the art is high, there are situations in which disclosure of **just one** species adequately supports a genus. The Written Description Guidelines state:

> A 'representative number of species' means that the species which are adequately described are representative of the entire genus. . . [T]here may be situations where one species adequately supports a genus. **What constitutes a 'representative number' is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by members of the genus in view of the species disclosed**.

As discussed above, Applicants have disclosed a large number of species to support the recitation of Non-Immunogenic, High Molecular Weight Compounds and Lipophilic Compounds (e.g., cholesterol, phospholipids, glycerolipids, glycerol amide lipids, liposomes,

polyalkylene glycol (including polyethylene glycol)). Further, Applicants have provided preferred molecular weight ranges for a number of these species, namely, "between approximately 1000 Da to 1,000,000 Da", at page 22, lines 12-26. The necessary common features, i.e., that of being high molecular weight, non-immunogenic, and/or lipophilic, with a molecular weight of between approximately 1000 Da to 1,000,000 Da, has been provided by Applicants.

Accordingly, Applicants submit that the genus corresponding to Non-Immunogenic, High Molecular Weight Compounds and Lipophilic Compounds has been supported with a representative number of species, in view of the skill and knowledge in the art.

With respect to Claim 8, the Examiner contends that the method is directed to targeting a therapeutic or diagnostic agent to a specific predetermined biological target that is expressing PDGF in a patient. The Examiner further contends that the specification does not describe how the site of delivery is predetermined, and contends that if the site of delivery is predetermined, it is not described if the target is meant to be the exclusive site of delivery. Further, the Examiner alleges that the specification does not provide any examples of delivery of a therapeutic agent covalently linked to a nucleic acid ligand complex to a target within a patient.

Applicants point out that in contrast to the Examiner's statements, the specification does in fact provide several examples of delivery of a therapeutic agent covalently linked to nucleic acid ligand to a target within a patient. In Example 7, for example, Applicants describe an experiment performed where a PDGF-binding nucleic acid ligand (NX31975) was conjugated to 40 kD polyethylene glycol, and the conjugate was delivered to Sprague-Dawley rats via I.P. injections. The rats had experimentally induced arterial lesions, which express PGDF, resulting in neointima formation. Neointima formation was reduced significantly (50%) in the treated rats. In the specification, it is disclosed that PDGF is a growth factor and is generally not expressed in the absence of proliferation such as that seen in restenosis, cancer, fibrosis, angiogenesis, or wound healing. See page 9, line 6 through page 13, line 24. In healthy adult rats, therefore, PDGF is not being expressed in appreciable amounts, except where the arterial lesions were induced, and this experiment shows that the conjugate was targeted to the arterial lesions (where PDGF was being expressed).

In Example 8 and 9, the conjugate as described in Example 7 was injected intravenously into Wistar rats having induced proliferative glomerulonephritis. Results showed that histological changes associated with mesangioproliferative changes (induced by PDGF) in the rat were markedly reduced and almost normalized in the NX31975-ligand group.

With respect to the Examiner's contention that the specification "does not describe how the site of delivery is predetermined", Applicants contend one of skill in the art would understand that a delivery site is a site that is expressing PDGF. In the background section, Applicants describe a number of proliferative diseases that are associated with expression of PDGF (a growth factor). PDGF is described as being associated with malignant transformation (cancer), cardiovascular disease, in particular, smooth muscle cell proliferation, renal disease (glomerular mesangial cell proliferation and matrix accumulation), among others. Applicants submit that the specification teaches that PDGF is associated with the cellular proliferation conditions in the above-described proliferative diseases and conditions and those diseases may be treated with the PDGF ligands of the invention. Accordingly, the specification teaches that the site of delivery is the tissue that is expressing PDGF in the patient. Further, such site is "predetermined" in that the clinician will be aware of the particular proliferative disease or condition the patient has or may have prior to treatment with or diagnostic application of the PDGF ligands of the present invention. However, in the interest of expediting prosecution, Applicants have removed the term "predetermined" in order to increase clarity.

In response to the Examiner's contention that "it is not described if the target is meant to be the exclusive site of delivery", by definition, a PDGF ligand of the instant invention is not a PDGF ligand unless it binds to PDGF with a binding constant that allows for a binding interaction at physiological pH and conditions. Implicit in the definition (and shown in the Examples where binding to other growth factors is not observed, see Example 9) is that the binding is specific, i.e., the binding affinity of the ligand for PDGF will be several orders of magnitude greater than for other compounds, such as, for example, other growth factors. Accordingly, one of skill in the art will understand the specification as disclosing that the target will be a site or tissue where PDGF is being expressed and that the binding of the ligand to the target will be thus highly specific to that site or tissue. Binding of the ligand of the invention to sites other than the target (these sites lacking expression of PDGF) will be significantly less than the binding to sites expressing PDGF. Accordingly, one of skill in the art will understand that the target is meant to be the exclusive site of delivery of the ligand of the present invention. However, it is submitted that minor amounts of non specific binding of the ligand of the invention to non-target tissues or sites will not be material to the invention and therefore clarification of whether the binding is exclusive or not is not necessary.

For the foregoing reasons, Applicants respectfully submit that the specification meets the written description requirement of Section 112, and request that the rejection be withdrawn.

Rejections under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 7 and 8 under 35 U.S.C. 103(a) as being unpatentable over Gold *et al.* (U.S. 5,270,163) in view of Tullis (WO 88/09810) and Ferns *et al.* (Science 1991, vol. 253, pages 1129-1132). The Examiner contends that Gold *et al.* teach a method for identifying nucleic acid ligands by a process of *in vitro* selection and amplification; that Tullis teaches nucleic acid conjugates comprising an antisense conjugated to a solubility modifying moiety that may be hydrophobic; and that Ferns *et al.* teach that inhibition of PDGF is a possible approach for prevention of restenosis following angioplasty.

Applicants note that when applying 35 U.S.C. 103, the following tenets of patent law must be adhered to: (A) The claimed invention must be considered as a whole; (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention and (D) Reasonable expectation of success is the standard with which obviousness is determined. *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

Applicants traverse this rejection. Applicants respectfully submit that the combination of the references does not render claims 7-8 obvious for the reason that the references do not suggest the desirability of making the combination, and the Examiner is using impermissible hindsight to make his argument. In particular, Applicants argue that the skilled person in the art would not have a reasonable expectation of success with the combination, for the reason that the Nucleic Acid Ligands of Gold *et al.* are not the functional equivalents of the oligonucleotides of Tullis and therefore there is no expectation of success in the substitution of the Nucleic Acid Ligands of Gold *et al.* into the teachings of Tullis and Ferns *et al.*

Specifically, there are distinct differences between Tullis' nucleic acid molecules (which act through a mechanism which predominantly depends on Watson/Crick base pairing or triple helix binding), and Nucleic Acid Ligands. Of importance is that the functionality of Tullis' nucleic acids is not dependent on their three-dimensional structure.

Tullis' antisense oligonucleotides act through hybridization (i.e., through Watson/Crick base pairing) with other nucleic acids (mRNA or genes). This is a two dimensional interaction. The Nucleic Acid Ligands of the subject invention bind to a non-nucleic acid target molecule (typically a protein). This is a three dimensional interaction.

Because the Nucleic Acid Ligands of the instant invention form specific binding pairs with their target molecule it is essential that they maintain their three-dimensional structure. Thus, even if assuming for the sake of argument that it may have been "obvious to try" conjugating a non-immunogenic compound, such as PEG, for intracellular delivery of a Nucleic Acid Ligand, success is not at all assured. Success is dependent on the Nucleic Acid Ligand maintaining its three-dimensional structure and thus its activity and/or affinity to the target while conjugated to PEG, a much larger moiety. Other than being both made up of the same basic four bases, nucleic acid ligands have no commonality with nucleic acids which act through hybridization. The two dimensional structure (other than determining three dimensional structure) does not mediate the functional effects of the Nucleic Acid Ligands of the invention. Accordingly, the art cited by the Examiner does not suggest or teach conjugating PEG to Nucleic Acid Ligands, which act through completely different mechanisms than the Tullis nucleic acids, nor is there an expectation of success for the combination. Whether the three dimensional structure (and resulting function) would be retained by the Nucleic Acid Ligands as demonstrated by Applicants in the instant invention was completely unpredictable and therefore there would be no expectation of success for the combination.

Applicants respectfully submit, therefore, that there is no expectation of success in the combination, in that it would not be expected or predicted that a Nucleic Acid Ligand in association with a Non-Immunogenic, High Molecular Weight Compound or Lipophilic Compound would retain the three dimensional structure required for affinity to PDGF from the combination of Gold *et al.* teaching Nucleic Acid Ligands; Tullis teaching an antisense nucleic acid conjugated to a solubility modifying moiety that may be hydrophobic; and Ferns *et al.* teaching that inhibition of PDGF is a possible approach for prevention of restenosis following angioplasty.

As an additional point, Applicants submit that it is well known in the art that in general, conjugating polyethylene glycol to ligand molecules may, due to the steric hindrance caused by the extremely large PEG molecule (with a size between 1000 Da and 1,000,000 Da), result in conjugates having variable, and in some cases no, reduction in affinity for target. Accordingly, in general, it cannot be predicted that "PEGylating" a ligand will necessarily result in a molecule retaining a useful binding affinity for the target, and each conjugate must be tested to determine whether the binding affinity has been altered. In view of this unpredictability, Applicants submit that in general, that there is no expectation of success in the combination.

Further, there is no suggestion in the references for a method for improving the pharmacokinetic properties of a PDGF Nucleic Acid Ligand by covalent association with a Non-Immunogenic, High Molecular Weight Compound or Lipophilic Compound in order to prevent restenosis following angioplasty. Applicants maintain therefore that claims 1-4 and 19 are not rendered obvious by the Tullis reference and respectfully request withdrawal of this rejection. Applicants respectfully submit that the Examiner is engaging in hindsight reconstruction.

If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to deposit account No. 19-5117 if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-5117.

Respectfully submitted,

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